NANOEMULGEL: A COMPREHENSIVE REVIEW ON THE RECENT ADVANCES IN TOPOCAL DRUG DELIVERY

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ABSTRACT
Many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage form are referred as emulgel. In recent years, there has been great interest in the use of novel polymers. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Emulgel are having major advantages on novel vesicular systems as well as on conventional systems considering various aspects. Numerous permeation enhancers can potentiate the effect of decreasing skin barrier resistance on the other hand promoting solubility of the drug in vehicle is also feasible. The use of emulgels can be considered well in analgesics and antifungal drugs. Emulgels are of two types micro emulsion gels and nano emulgel.

KEYWORDS: Emulgels, Topical drug delivery, Cosmetology, Hydrophobic Drug, Polymer, Chronic Skin Diseases.

INTRODUCTION[1-4]

Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water soluble drugs. In short emulgels are the combination of emulsion and gel. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used, so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In recent years, there has been great interest in the use of novel polymers which can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In cosmetics, such as hydrophilic systems have already been known for a longer
period and their wide utilization as pharmaceutical dosage form comes from the wide utilization as pharmaceutical dosage form comes from wide utilization of emulsions systems particularly for dermatological formulae. Emulgel is defined as the emulsion either o/w or w/o type, which is gelled by mixing it with gelling agent like (HPMC or Carbomer). Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outer most layer is the rate limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, water soluble ions and polar molecules do not penetrate intact stratum corneum. Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and antibacterials help a damaged barrier toward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer. During development of semi-solid preparations for coetaneous application whose formulation contains an antimicrobial preservative, the need for and the efficacy of the chosen preservative shall be demonstrated to the satisfaction of the competent authority.

**Advantages of Emulgel**[^5-6]

- Avoidance of systemic adverse effects of drug i.e. first pass metabolism in the body.
- Systemic circulation is minimized or prevented.
- Improve patient compliance and acceptability.
- Suitable for self-medication.
- Provide target drug delivery on the body.
- Ability to easily terminate medication.
- Can easily pass through skin having dual behavior i.e. hydrophobic as well as hydrophilic.

[^5-6]: Bhavesh et al. / Pharma Science Monitor 7(2), Apr-Jun 2016, 346-355
They are convenient to apply on hairy skin due to absence of greasiness and lack of residues upon application.

**Disadvantages of Emulgel**

- Skin irritation on contact dermatitis.
- Bubbles formed during emulgel formulation.
- Possibility of allergenic reactions.
- Drugs having large particle size (>400 daltons) are not easily absorb or cross through the skin barrier.

**Material Use For The Preparation Of Emulgels**

1. **Aqueous Material:**
   This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.

2. **Oils:**
   These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are non biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.

3. **Emulsifiers:**
   Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. e.g Polyethylene glycol 4031 stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

4. **Gelling Agent:**
   These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.

5. **Permeation Enhancers:**
   These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

**Method of preparation of emulgels**

**Step-1**
Drugs are incorporated into either oil or aqueous phase depending upon its solubility.

**Step 2**
Formation of gel base.

**Step 3**
Incorporation of emulsion in gel base.

**Preparation of gel phase:**
The gel phase in the formulations is prepared by dispersing polymer in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5 using triethanolamine (TEA).
Preparation of oil phase of emulsion:
Oil phase of the emulsion is prepared by dissolving emulsifier e.g. span 20 in oil phase like light liquid paraffin.

Preparation of aqueous phase:
The aqueous phase is prepared by dissolving emulsifier e.g. tween 20 in purified water.

Preparation of drug solution:
The drug is dissolved in ethanol.

Characterisation of emulgel\cite{17-25}:

1. Physical examination
The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation. The pH values of 1% aqueous solutions of the prepared gellified emulsions were measured by a pH meter (Digital pH meter DPH 115 pm).\footnote{1}

2. Rheological studies
The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

3. Globule size and its distribution in emulgel:
Globule size and distribution are determined by Malvern zetasizer. A 1gm sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is injected into photocell of zetasizer. Mean globule diameter and distribution is obtained.

4. Spreading coefficient
Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80g. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability.
5. Extrudability study of topical emulgel (tube test)

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

\[ \text{Extrudability} = \frac{\text{Applied weight to extrude emulgel from tube (in g)}}{\text{Area (in cm}^2)} \].

6. Swelling index

To determine the swelling index of prepared topical emulgel, 1 g of gel is taken on porous aluminium foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

\[ \text{Swelling Index (SW)} \% = \frac{(Wt - Wo)}{Wo} \times 100. \]

Where, (SW) \% = Equilibrium percent swelling,
Wt = Weight of swollen emulgel after time t,
Wo = Original weight of emulgel at zero time.

7. Drug content determination

Take 1g of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

\[ \text{Drug Content} = (\text{Concentration} \times \text{Dilution Factor} \times \text{Volume taken}) \times \text{Conversion Factor} \]

8. Skin irritation test (patch test)

The preparation is applied on the properly shaven skin of rat and its adverse like change in colour, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

9. Ex-vivo bioadhesive strength measurement of topical emulgel
(MICE SHAVEN SKIN): The modified method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slides is fixed on then wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left hand pan. 1 g of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200mg/min to the left hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following formula.

\[
\text{Bioadhesive Strength} = \frac{\text{Weight required (in gm)}}{\text{Area (cm}^2\text{)}}
\]

10. Invitro release study
Franz diffusion cell (with effective diffusion area 3.14 cm² and 15.5 ml cell volume) is used for the drug release studies. Gellified Emulsion (200 mg) is applied onto the surface of egg membrane evenly. The egg membrane is clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared PBS (pH 5.5) solution to solubilise the drug. The receptor chamber is stirred by magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time interval. Samples are analyzed for drug content by UV visible after appropriate dilutions. Cumulative corrections are made to obtain the total amount of drug release at each time interval .The cumulative amount of drug released across the egg membrane is determined as a function of time.

11. Microbiological assay:
Ditch plate technique is used. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates are used. Three grams of the Gellified emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth is observed and the percentage inhibition is measured as follows.

\[
\% \text{ inhibition} = \frac{L_2}{L_1} \times 100
\]

Where \( L_1 \) = total length of the streaked culture
\( L_2 \) = length of inhibition
12. Drug release kinetic study

To analyse the mechanism of drug release from the topical gel, the release data were fitted to following equations

**Zero – order equation:**

\[ Q = K_0 t \]

Where Q is the amount of drug released at time t, and \( K_0 \) is the zero – order release rate.

**First – order equation:**

\[ \ln(100 - Q) = \ln 100 - K_1 t \]

Where Q is the percentage of drug release at time t, and \( K_1 \) is the first – order release rate constant.

**Higuchi’s equation:**

\[ Q = K_2 \sqrt{t} \]

Where Q is the percentage of drug release at time t, and \( K_2 \) is the diffusion rate constant.

13. Stability studies

The prepared emulgels were packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profile.

14. Accelerated stability studies of Gellified emulsion:

Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples were analysed for drug content every two weeks by UV-Visible spectrophotometer. Stability study was carried out by measuring the change in pH of gel at regular interval of time.

**Current Pharmaceutical Products Available in Market.**

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Product Name</th>
<th>Drug Compound</th>
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<tbody>
<tr>
<td>1.</td>
<td>MiconazHemulgel</td>
<td>Miconazole Nitrate and Hydrocortisone</td>
</tr>
<tr>
<td>2.</td>
<td>Rapamune</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>3.</td>
<td>Triglide</td>
<td>Fenofibrate</td>
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CONCLUSIONS

Emulgels being a recent technique for topical drug delivery is also beneficial in incorporating hydrophobic drugs as well as a good choice for combination of both hydrophilic and hydrophobic drugs. In next few years, topical drug delivery will be used extensively in order to impart patient compliance and since emulgels have non greasy, gel like property along with relatively good drug release rates they may be used popularly as novel topical drug delivery formulations in future. Since emulgels possesses an edge in terms of spreadibilty, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in an water soluble gel bases. Emulgel is helpful in enhancing Spreadability, adhesion, viscosity and extrusion, this novel drug delivery will become a popular formulation in future.

REFERENCES

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